

Immunology and Skin Disease 2009: Frontiers in Cutaneous Immunology

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In March 2009, the course entitled Immunology and Skin Disease 2009: Frontiers in Cutaneous Immunology was held in Boston, Massachusetts.* Ninety-eight physicians and scientists from 13 countries attended. Organized by Robert Fuhlbrigge and Rachael Clark (Harvard University, Boston, MA), the course covered the latest developments in cutaneous immunology. Thomas Kupper (Harvard University) began by quoting Albert Szent-Györgyi: “Discovery is seeing what everybody else has seen, and thinking what nobody else has thought.”

Michael Zasloff (Georgetown University, Washington, DC) presented a fascinating overview of antimicrobial peptides (AMPs), small proteins produced by epithelial cells that provide front-line protection against skin pathogens. The AMP repertoire varies at different body sites and reflects differing skin flora at these sites. Vitamin D induces production of the AMP LL-37, and this molecule, together with Toll-like receptor (TLR) activation, enhances the ability of macrophages to kill mycobacteria. The underproduction and overproduction of AMP are associated with human diseases. Atopic dermatitis patients have decreased levels of AMP and frequent skin infections. AMPs are overproduced in psoriatic skin, and individuals with increased copy numbers of β -defensin AMP genes are at increased risk for developing the disease. A complex of self-DNA and LL-37 stimulates activation of plasmacytoid dendritic cells (pDCs), a critical event in the initiation of psoriatic lesions.

Antigen-presenting cells (APCs) are critical to the initiation and tuning of T-cell responses. Georg Stingl (Medical University of Vienna, Austria) described three types of APCs in the skin. Studies on genetically modified mice suggest that epidermal Langerhans cells suppress T-cell responses and promote tolerance, contrary to earlier reports. Dermal DCs, on the other hand, elicit potent immune reactions when antigen is taken up under conditions that induce DC maturation. pDCs are scarce in normal skin, frequent in inflamed skin, and, together with a subtype of myeloid DCs, accumulate in imiquimod-treated skin. Both imiquimod-induced myeloid DCs and pDCs express molecules of the lytic machinery, kill cancer cells *in vitro*, and may be responsible for imiquimod-induced regression in basal cell carcinomas (BCCs). Based on recent evidence, Stingl and his co-workers propose that TLR7-activated pDCs may contribute to the apoptotic death of activated T cells in HIV infection.

APCs and other cells sense pathogens via TLRs, a set of pathogen receptors hard-wired into the genome. Michael Schön (Georg August University, Germany) described how these highly conserved receptors signal through MyD88, and have a common double-arched shape despite the differing structures of their ligands. TLRs can induce both stimulatory and inhibitory signals, and TLR signaling contributes to autoimmune diseases, including lupus erythematosus and inflammatory bowel disease. Stimulation of TLR9 from the apical surface of intestinal cells downmodulates inflammatory

NF κ B signaling, but stimulation from the basal surface is proinflammatory. TLR7/8 agonists such as imiquimod are used to treat actinic keratoses and BCC; Schön showed striking photos of cutaneous metastases of malignant melanoma that cleared after topical imiquimod therapy. In addition to TLR7/8 signaling, imiquimod can activate cells via adenosine receptors and can induce tumor cell death directly.

DCs travel to lymph nodes, where they present antigens to T and B cells. Using intravital microscopy in anesthetized mice, Ulrich Von Andrian (Harvard University) observed that T cells interacting with antigen-laden DCs progressed through three stages. They first made brief serial contacts with many DCs and became activated. They then formed stable, long-lasting contacts with a single DC and developed cytokine production and effector functions. Finally, they again made brief contacts with multiple DCs and proliferated. These stages—dating, mating, and procreating—allowed T cells to scan multiple DCs and integrate these signals into a single decision to respond or not. Von Andrian also reported that macrophages present in the subcapsular sinus of lymph nodes trap particulates, including viruses, and then present these particles to lymph node B cells.

Regulatory T (Treg) cells and IL-17-producing T helper (Th17) cells are two recently described T-cell subsets with reciprocal roles. Treg cells induce and maintain self-tolerance. Th17 cells not only defend against extracellular pathogens but also contribute to

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inflammatory diseases such as arthritis and psoriasis. Estelle Bettelli (Harvard University) presented studies of experimental autoimmune encephalomyelitis in mice, a Th17- and Th1-mediated disease. IL-6 promoted Th17 development and inhibited formation of Treg cells. Transforming growth factor- β (TGF- β), IL-21, and IL-23 also drove pathogenic Th17 cells. Similar findings have been reported in psoriasis. DCs and keratinocytes in psoriatic lesions overproduce IL-23, driving the development and proliferation of Th17 cells. These cells, in turn, produce IL-22 and other inflammatory mediators. IL-22 induces keratinocyte proliferation and acanthosis in the epidermis. These studies suggest that interruption of IL-23 signaling or Th17 effector function might benefit patients with any of several different inflammatory disorders.

Few topics have received more attention recently than vitamin D. Several studies show that the majority of people in the United States are vitamin D deficient, especially in winter. Dermatologists must walk a fine line in recommending sun protection for vulnerable patients while ensuring that they obtain adequate vitamin D. Daniel Bikle (University of California, San Francisco) spoke about recent findings that vitamin D plays a critical role in immune responses. It stimulates the production of AMPs by skin, and, upon stimulation, macrophages can generate their own vitamin D, enhancing their ability to kill pathogens. Vitamin D also promotes the differentiation of Th2 and Treg cells, inhibits the differentiation of Th17 cells, and helps to imprint T cells with skin-homing addressins. Recent studies suggest that 2,000 units of vitamin D per day may be required to obtain adequate blood levels, but optimal dosage varies from patient to patient.

Hilde Cheroutre (La Jolla Institute for Allergy and Immunology, San Diego, CA) presented evidence that retinoic acid (RA), a derivative of vitamin A, plays a critical role in gastrointestinal immunity. RA produced by gut DCs induces T-cell expression of gut-homing addressins. RA promotes the development of Treg cells, suppresses IL-17 production, and,

together with TGF- β , can repolarize Th17 cells to a regulatory phenotype. Thus, under normal conditions, RA helps to drive T-cell immunity toward the formation of tolerogenic Treg cells. In mice, a population of CD4 T cells coexpresses CD8 $\alpha\alpha$ after exposure to the gut microenvironment. Under normal conditions, the activity of these cells is suppressed, but CD8 $\alpha\alpha$ T cells can become highly cytotoxic when exposed to inflammation. Thus, reprogramming at peripheral tissue sites supports the generation of tolerogenic T cells at baseline, but mechanisms exist that allow these T cells to become highly cytotoxic if necessary.

In his keynote address, David Altshuler (Harvard University) described how genome-wide genetic mapping allows the linkage of disease states to genetic alleles expressed by affected individuals. Technology-driven improvements have allowed a shift from hypothesis testing to hypothesis generation. Instead of confirming the role of previously identified gene products, these screens allow the identification of previously unsuspected molecules that can then be tested as drug targets. Small population variations in a clinical measurement can allow the identification of gene products that, if inhibited completely, may have a substantial clinical effect, because population studies determine the effect of a particular allele on a clinical parameter, not the effect of complete inhibition of a particular gene product. New developments in sequencing technology are expected to rapidly increase the scope and power of these approaches.

Jiali Han (Harvard University) presented his work on genome-wide genetic mapping of polymorphisms conferring susceptibility to skin cancer. Han gathered data from the Nurses Health Study, a cohort of over 120,000 women followed since 1976. Risk-factor data were collected prior to disease development. Blood samples from women who developed skin cancer were compared with age-matched controls. Polymorphisms in the *MC1R* gene associated with pheomelanin (red hair) conferred increased risk for both melanoma and nonmelanoma skin cancers, and *MC1R* variants

helped the researchers predict the development of melanoma and BCC in other patient populations. Han's work illustrates how genome-wide genetic mapping can be used both to study the underlying biology of a disease and to predict disease development in patient populations.

Gregory Lanza (Washington University, St. Louis, MO) described his cutting-edge work with fluorocarbon nanoparticles. Highly visible by MRI or ultrasound, proteins can be added to target these particles specifically (for instance, to areas of angiogenesis in tumors or sites of inflammation). Medications can also be incorporated and delivered directly to targeted cells. Specifically, $\alpha v \beta 3$ -integrin targeted nanoparticles filled with the angiogenesis inhibitor fumagillin inhibited angiogenesis in rabbit breast cancers and clinically improved arthritis in mouse models. Nanoparticles can be used to visualize angiogenesis, inhibit it, and then monitor responses to therapy. Lanza described photoacoustic tomography, a new technology in which a laser pulse excites skin or another tissue and the resultant vibrations are detected by ultrasound. Using gadolinium-enhanced nanoparticles, this method allowed noninvasive sentinel lymph node mapping in rats and has many promising dermatological applications.

Psoriasis and atopic dermatitis, two common inflammatory skin diseases, were addressed next. Brian Nickoloff (Loyola University, Chicago, IL) discussed the changing focus of psoriasis research. Initially focused solely on keratinocytes, psoriasis researchers now understand that plasmacytoid DCs and Th17 T cells play a critical role in the pathogenesis of this disease. Thomas Bieber (University of Bonn, Germany) presented an elegant discussion of atopic dermatitis (AD) with an emphasis on personalized medicine. AD is a clinically and genetically heterogeneous disease. Genes predisposing to AD fall into two broad categories: skin-related genes that affect barrier function and atopy-related genes that affect the tendency of an individual to be allergic. Polymorphisms in the filaggrin gene that impair skin barrier

function and changes in the gene for IL-4 and its receptor are all associated with AD. Knowledge of an individual's risk alleles could be used to tailor therapy and to identify individuals at risk for progressive sensitization, allowing early intervention to improve barrier function. Epigenetic changes may explain why some individuals develop AD later in life, and the environment also plays a critical role. AD skin shows residual signs of inflammation even between flares. Proactive intermittent use of steroids or calcineurin inhibitors significantly decreases both the frequency and severity of flares.

Rachael Clark (Harvard University) noted that a minority of patients with cutaneous T-cell lymphoma (CTCL) develop rapid and fatal disease progression. Differentiating these high-risk patients from the majority who do well is difficult. Clonal T cells with chromosomal abnormalities are present in both early and advanced CTCL, suggesting that genetic damage is a common feature. Marked loss of T-cell diversity often occurs, indicating widespread T-cell death on a par with HIV disease. Neutrophils are activated, and *Staphylococcus aureus*-driven inflammation of T cells worsens the disease. Extracorporeal photopheresis improves CTCL, but evidence suggests that it does so by inducing tolerance. New findings in skin T-cell biology explain some but not all features of the disease, and a unifying hypothesis remains elusive.

Smallpox vaccination, which involves scarification of the skin, is the most effective vaccination in recorded history. Luzheng Liu (Harvard University) described studies showing that scarification provided enhanced systemic immunity and protection against skin and respiratory challenge in vaccinia-immunized mice. Following scarification, T cells entered the skin-draining lymph node and generated effector cells expressing skin-homing receptors. Early on, antigen-specific cells also seeded other lymph nodes and gave rise to additional effector populations able to access other tissues. Liu's work suggests that scarification is a safe and highly effective vaccination route capable of inducing potent and widely disseminated immune protection.

James Campbell (Harvard University) described his work on T-cell homing to skin in mice. He pointed out that a T cell's homing receptor expression should be considered separately from its functional characteristics because the chemokine profile of a T cell indicates its homing characteristics but does not define its functional differentiation (e.g., Th17). Recent studies have shown that immunization via the skin gave rise to T cells with skin-homing phenotypes, whereas immunization through the gut generated gut-homing T cells. CCR4 is a chemokine receptor expressed by T cells in human and mouse skin, but it is also expressed by

noncutaneous T cells. This raises the question of whether CCR4 functions as a skin-homing receptor. Using CCR4-deficient mice, Campbell demonstrated that CCR4 plays a critical role in supporting T-cell entry into the skin.

The meeting concluded with a fascinating presentation by Robert Sackstein (Harvard University) on mesenchymal stem cells (MSCs). In contrast to embryonic stem cells, MSCs can be obtained from adult bone marrow and do not form teratomas. MSCs have many natural functions, including the formation of vascular pericytes. They can also enhance tissue repair and are markedly immunosuppressive. MSCs secrete nitric oxide, produce indolamine 2, 3-dioxygenase and prostaglandin E_2 , and suppress mixed leukocyte reactions. MSCs from unrelated donors can halt the progression of severe graft-versus-host disease in critically ill patients. By inducing the formation of the carbohydrate HCELL on cell surfaces, Sackstein targeted intravenously infused MSCs to the bone marrow with the goal of enhancing bone production, a possible treatment for osteoporosis.

Fuhlbrigge concluded the course with thanks to the organizers, speakers, and attendees.

** Immunology and Skin Disease 2009: Frontiers in Cutaneous Immunology was held at the Fairmont Copley Plaza Hotel in Boston, Massachusetts, USA, 19–21 March 2009.*

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